Epilepsy & Behavior 72 (2017) 108–113

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical Research

Accelerated Long Term Forgetting in patients with focal seizures: Incidence rate and contributing factors

Laurie A. Miller [a,b,*], Annu Mothakunnel [b,c], Emma Flanagan [c,d], Armin Nikpour [a,b], Zoe Thayer [a,b]

[a] Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, and Central Medical School, University of Sydney, Camperdown, NSW, Australia
[b] ARC-Centre of Excellence in Cognition and Its Disorders, University of Sydney, NSW, Australia
[c] Neuroscience Research Australia, Sydney, NSW, Australia
[d] Norwich Medical School, University of East Anglia, Norwich, United Kingdom

ARTICLE INFO

Article history:
Received 17 January 2017
Revised 21 March 2017
Accepted 22 April 2017
Available online 7 June 2017

Keywords:
Memory
Epilepsy
Lateralization
Hippocampus
Temporal lobe
Anticonvulsant

ABSTRACT

Background: Accelerated Long Term Forgetting (ALF) is usually defined as a memory impairment that is seen only at long delays (e.g., after days or weeks) and not at shorter delays (e.g., 30 min) typically used in clinical settings. Research indicates that ALF occurs in some patients with epilepsy, but the incidence rates and underlying causes have not been established. In this study, we considered these issues.

Methods: Forty-four patients with a history of focal seizures were tested at 30 min and 7 day delays for material from the Rey Auditory Verbal Learning Test (RAVLT) and Aggie Figures Test. Recently published norms from a matched group of 60 control subjects (Miller et al., 2015) were used to determine whether patients demonstrated ALF, impairment at 30 min or intact memory performance.

Results: The incidence of ALF in the epilepsy patients (18%) was >3 times higher than normal on the RAVLT, but no different (7%) from the incidence in normal subjects on the Aggie Figures. A different, but again significantly high, proportion of patients (36%) showed shorter-term memory deficits on at least one task. ALF was found mainly in patients with temporal-lobe epilepsy, but also occurred in one patient with an extratemporal seizure focus. Presence of a hippocampal lesion was the main predicting factor of ALF.

Conclusions: Many patients with a focal seizure disorder show memory deficits after longer delays that are not evident on standard assessment. The present study explored the factors associated with this ALF memory profile. These new findings will enhance clinical practice, particularly the management of patients with memory complaints.

1. Introduction

Accelerated Long Term Forgetting (ALF) is a relatively newly described memory disorder in which a person shows good retention over a short period (e.g., up to 30 min), but then forgets at a rapid rate over the next few days or weeks [2,3]. This phenomenon has most often been reported in patients with temporal-lobe epilepsy [4,5] or transient epileptic amnesia [6,7]. Given the nature of standard memory testing, which typically involves shorter delays only, this type of longer-term memory disorder has gone largely undetected in clinical practice until recently. It is important to identify ALF, however, because it may be the first sign of a neurological problem [8] and because subjective memory complaints tend to correlate with long-term retention rather than with short-term scores [9,10]. It is not yet clear what proportion of patients with focal seizures have ALF, because research results have generally been presented for individual case studies or as an average for a group. Understanding the incidence of ALF in focal epilepsy and factors that predict its occurrence would improve clinical perspective and potentially offer new insights into longer term memory processes.

Many studies of ALF have employed a learning-to-criterion technique to ensure equivalence of encoding across subjects. Under these conditions, patients often show intact memory over the initial, 20–30 min delay interval, but then demonstrate significant loss after days or weeks [4,9,11]. That is, as a group, their mean scores are indicative of ALF. This finding of relatively good memory at shorter delays, however, seems at odds with numerous previous reports of memory difficulties at these same, short delays in patients with temporal-lobe epilepsy [12–14], in particular when the hippocampus has been removed or is sclerotic [15–17]. It may be that this inconsistency in memory findings at 20–30 min delays is related to differences in learning condition (i.e., learned-to-criterion conditions of the more recent ALF studies versus limited exposure during learning in most of the earlier reports). We found support for this proposal when we compared these two learning conditions for stories; ALF was more evident when

* Corresponding author at: Neuropsychology Unit, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia.
E-mail address: laurie.miller@sydney.edu.au (L.A. Miller).

http://dx.doi.org/10.1016/j.yebeh.2017.04.039
1525-5050/

epilepsy patients had learned the material to criterion than when they heard the stories only once [18]. For the present study, we chose to use standardized memory measures that involve multiple (5) presentations during learning. Recall was then tested at 30 min and 7 day delays.

A recent review paper [19] identified several clinical factors associated with ALF. Interictal discharges are common in patients with ALF, though there is less evidence that seizures during the delay interval [9,20], side of epileptic focus [21–25] or underlying etiology [19] are influential. Site of brain abnormality is probably also important. Most patients identified as showing ALF have had abnormalities in the temporal lobe, though a few recent studies have indicated that patients with an extratemporal focus (i.e., one outside the temporal lobe) can also demonstrate ALF [18,26,27].

It was also noted that patients who present with complaints consistent with ALF and are found to have an epileptic condition (usually TEA) tend to be middle aged or older [19]. It will be interesting to determine whether patients with focal seizures who show ALF are older than those without ALF and/or whether they had a later age of seizure onset.

Because patients with epilepsy can be treated with a number of different antiepileptic drugs (AEDs) alone or in combination, researchers have generally been able to consider only whether the *number* of AEDs predicts ALF and this has not been found to be the case [9,20,26]. Whether any particular medications are more likely than others to cause ALF has yet to be determined.

Structural hippocampal abnormality has been linked both with deficient memory at short delays (20–30 min) [15,21,22] and with memory decay over 24 h [11,18]. After intervals of days or weeks, however, impairments in memory have *not* been found to be limited to patients with hippocampal lesions [10,18,26,28,29]. A comparison of the impact of a hippocampal lesion at short vs long term retention intervals will help elucidate its contribution to memory over time.

Given that memory for different types of material decays at different rates [7,30,31], incidence of ALF might also be affected by the type of to-be-remembered material. Although most previous studies have detected steeper long-term forgetting rates in people with focal seizures compared to control subjects for both visual and verbal materials [19], visual and verbal tasks have often not been well-matched. With this in mind, the present investigation used 15-item lists consisting of verbal (words) and nonverbal (abstract drawings) material learned and recalled under similar conditions. Earlier work indicated that healthy subjects learn a similar number of items from the two lists [32] and subsequently show similar recall scores for words and drawings at 30 min and 7 day delays [1]. We will now discover whether patients with focal seizures show similar forgetting rates for the two types of material.

By investigating memory task performance at short and long delays, we will determine what proportion of patients with focal seizures show ALF. The associated clinical and demographic characteristics will also be identified.

2. Methods

2.1. Ethics and consent

This study was approved by Royal Prince Alfred Hospital's Human Research Ethics Committee. All participants provided written informed consent.

2.2. Participants

2.2.1. Patients

Potential patients were approached to participate if they met the following inclusion criteria: (1) they were identified by A.N. (Clinical Neurologist) as having a focal seizure disorder on the basis of a full clinical work-up (i.e., EEG, neuroimaging, clinical history); (2) they spoke English; and (3) they had no neurological or psychiatric history other than epilepsy. After testing, any subjects with an estimated Full Scale IQ below the average range (i.e., <80) were excluded.

Based on clinical interview, age of epilepsy onset, time since onset and frequency of seizures were established. Number and types of AEDs were also recorded. Fifty-one patients were tested initially but 6 failed to complete the testing after a 7-day delay. One additional subject was excluded because her estimated Full Scale IQ fell below 80. Twenty-two male and 22 female participants comprised the final group of 44. A.N. (blind to the neuropsychological results) determined the side and site of epileptic focus as well as the presence of a hippocampal lesion ($n = 17$).

One patient who had evidence of both left- and right-sided abnormalities was excluded from analyses comparing effects of lesion side. Three patients with temporal *plus* extratemporal abnormalities were not included in the analyses comparing effects of lesion site.

2.2.2. Normal control (NC) subjects

The group of 60 subjects (without neurological or psychiatric history) from our normative study served as a comparison group [1].

2.3. Neuropsychological test materials

2.3.1. Rey Auditory Verbal Learning Test (RAVLT) [33]

A 15-item word list (List A) is presented over 5 learning trials. In each trial, the list is read aloud to the subject and they are asked to recall as many words as possible. A distractor list of 15 new items (List B) is then read by the examiner and recalled by the subject in a similar fashion (but only once), and an unprompted ("immediate") recall of List A follows. Thirty minutes later, the delayed recall of List A is requested. For this study, subjects were also called 7 days later (without warning) and long term recall of List A was collected over the telephone. The number of words remembered after 30 min served as the 30 min Recall Score and the Percent Change Score was calculated as: [(number recalled at 30 min − number recalled at 7 days) / recall at 30 min] × 100.

2.3.2. Aggie Figures [32].

This test of memory for a set of 15 abstract line-drawings was created to be a visual analogue of the RAVLT and is presented in a similar fashion. Each line-drawing of List A is shown to the subject for a few seconds, one after another, using a ring-bound booklet. After seeing all 15 items, subjects are provided with a blank sheet of paper and asked to draw as many as possible. This is repeated for 5 learning trials, and then a distractor list (List B) of 15 new drawings is presented and recalled. Immediate and 30 min delayed recall of List A follows. At the time of the phone call seven days later, subjects were instructed to draw again all the figures they could remember and then post back the sheet. Subjects had not been forewarned that their recall would be retested. The number of figures remembered after 30 min served as the 30 min Recall Score and the Percent Change Score was calculated as: [(number recalled at 30 min − number recalled at 7 days) / recall at 30 min] × 100.

2.3.3. Test of Premorbid Functioning (TOPF) [34]

The TOPF is a measure of reading pronunciation ability for words that have irregular grapheme-to-phoneme translation. The number correct is converted to an estimate of Full Scale Intelligence Quotient (FSIQ) on the Wechsler Adult Intelligence Scale IV using age-adjusted norms.

2.3.4. Depression Anxiety Stress Scale (DASS-21) [35]

This is a 21-item self-report questionnaire measuring symptom frequency in the last week with regard to depression, anxiety and stress. Upon completion, scores are doubled to match the original 42-item version on which the norms are based. Only the score for the depression symptoms items (DASS-D) was used in this study. A score of 10 or higher suggests at least mild depression.